Number of pages (inc. cever sheet) 36

Date 4/20/17

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FAX COVER SHEET

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571-273-3664

Fax number

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Figh

973-422-7695 Phore aumber

Fax number

Organon - IP

Copies to Subject

973-422-7474 Reference

As requestac for printing curposes attached is a substitution specification for U.S. application. Ser. No. 10/518,279 (Case 2002.755). No new matter has ocen added to this application. U.S. app loat on Ser. No. 10/518,279 (Case 2002.735) Substitute Specification:

Respectfully submitted,

Suran Hero

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I-{(INDOL-3-YL)CARBONYLJPIPERAZINE DERIVATIVES

The present invertion relates to 1-[(Indo\3-yl),carbory||piperazine derivatives, to phermaceutical compositions comprising the same and to the use of these 1-{(indo-3-yl)carbony||oiperazine derivatives as cannabloold agonists in the treatment of pain and other disorders.

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1-{(Indol-3-yi)carbony|]p.pe.azine der vativəs are kncwn as compounds endowed with interesting pnemacological properties. 1-{(Indol-3-yi)carbony|]piperazine derivatives with unsubstituted indole nitrogen atom are discussed in WO9806715 (SmithKlireBeecham Corp.) as anti-inflammatory agents. Related 1-{(Indol-3-yi)carbony||piperazine derivatives which may also be substituted at the indole nitrogen atom are disclosed in WO0143746 (Nippon Shinyaku Co.) as compounds having antiinflammatory and nephrotropic activities.

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15 14(1-Benzyl-indok-3-yl)carbonyl]piperazine derivatives were disclosed in a study on H1-receptor antagonists (Battaglia, S. et al. *Eur. J. Med. Chem.* 34, 93-105, 1999) and in a study on anti-firfammatory agents (Dufics, M. et al. *Eur. J. Med. Chem.* 38, 245-553, 2001), and found to be of relatively low activity in both studies.

Recently '-{(ndol-3-yl)carbonylipiperazine derivatives were generically described in WO0158839 (Bristo-Myers Squibb) as being active modulators of the cannebhold receptor and as such useful in the treatment of respiratory diseases. No specific '- 'tindol-3-yl)carbony.]piperazine derivatives were disclosed in this patent application.

Pain treatment is often limited by the side effects of currently available medication.

For moderate to severe pain, opioids are widely used. These agents are cheap and effective but suffer from serious and potentially life-threatening side-effects, most notably respiratory depression and muscle rigidity. In addition, the doses of opioids which can be administered are limited by haused, emesis, constitution, prurits and uninary retention, often resulting in patients efecting to receive sub-optimal pain control rather than suffer these distressing side effects. Furthermore, these side-effects often result in patients requiring extended hospitalisation. Opioids are Highly addictive and are schaduled drugs in many territories. There is therefore a demand for hew analgesics that have an improved side effect profile compared to currently used products, at equi-aralgesic bases.

Evidence is accumulating thet cannabinoid agonists have potential as analgesic and inflammatory agents. Two types of cannab nod receptors are implicated, the

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cannabinoid CB1 receptor, which is located primarily in the central nervous system

but which is also expressed by peripheral neurones and to a lower enternt in other per pheral tissues, and the cannabincid CB2 receptor, which is mostly located in immune cells (Howlett, A.C. et al.: International Union of Pharmacology. XXVII. Classification of Carnabinoid Receptors Pharmacol. Rev. <u>54</u>, 161-202, 2002). While the CB2 receptor has been implicated in modulating the immune and ancillifarmatory response of carnabinoids, cannabinoid receptor agonists, especially those acting at the CB1 receptor have recently been suggested as useful in the treatment of pain (Iversen, L. and Chapman, V.: Cannabinoids: a real prospect for pain raise? Ourent Opinion in Pharmacology, <u>2</u>. 50-55, 2002 and references therein). Cannabinoid receptor agonists, such as CP 55,940 and WIN 55,212-2, produce potent antinoclosption with equivalent efficiacy to morphine in animal models of acute pain, persistent inflammatory pain and neuropathic pain. The known cannabinoid agorists are in general highly libophilic and insolube in water. There is a thus a need for carnab noid agonists with improved properties for use as therapeut cagents.

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o this end the present invention provides 1-(indol-3-yl)carbonylpiperazine derivatives having the general formula I

Formula I

wherein

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R represents 1-4 substituents independently selected from H. (C₁₋₄)zlkyl (cptionally substituted with halogen), iC₁₋₄)alkyloxy (cptionally substituted with halogen), halogen, OH, NH₂, CN and NO₂.

25 R₁ is (C₅₄)cycloalkył or (C_{5.E})cycloal kenyl;

R2 SH, nethyl prethy;

ીક, Rક, Rક, Fa', Rs, ીક and Rs'are independently hydrogen or (C₁.₄)alkyl, optionally substituted with (G₁.₄)alkylcxy, helogen or OH;

ેલ is hydrogen or (C. ાંઘીપુરા, optionally substituted with (C. ાં)alkyloxy, halogen or OH;

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Py forms together with R₆ a 4-7 membered saturated heterocyclic ring, optionally containing a further heteroatom selected from O and S; or R₇ is -1, (C₁₋₄)a kyl or (C₃₋₆)cyc oa kyl, the alkyi gracips being optionally substituted with OH, halogen or iC₁₋₄)alky oxy; or a pharmaceutically acceptable salt thereof, as agonists of the cannablooid receptor, which can therefore be used in the treatment of pain such as for example peri-operative pain, chronic pair, neuropathic pain, cancer pain and pain and spasificity associated with multiple sclerosis.

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Fe forms together with R, a 4-7 membered saturated reterocyclic ting, optionally

containing a fur.her heteroatom selected from O and S;

The fern (Ct.J)alkyl as used in the defirition of formula I means a branched or unbranched alkyl group having 1.4 carbon atoms, Ike buryl, Isobutyl, tentiary butyl, probyl, isopropyl, ethyl and methyl.

In the term (C₁₋₄)alkyloxy, (C₁₋₄)alkyl has the meaning as defined above.

The term (C₂₋₆)-ycloalkyl means a saturated cyclic alkyl group having 5-8 carbon atoms, and can thus represent cyclobentyl, cyclohexyl, cycloheptyl or cycloockyl. Preferred (C₆₋₆)-ycloalkyl groups are cyclopentyl and cyclohexyl.

The term (C₆₋₃)cycloa kenyl means a cyclic alkeny group having 5-8 carbon atoms 30 and at least one double bond, like cyclopent: 3-enyl or cyclohax-3-enyl.

The term halogen means F, Cl, Br or

In the definition of formula I R₆ can form together with R₇ a 4-7 membered saturated heterocyclic ring, which means that R₆ together with the carbon atom to which it is bound and R₇ together with the nitrogen atom to which it is bound complete a 4-7 membered saturated ring, such as an azettoine, a pyrrolidine, a pendine, or a 1H-azepine ring. Such rings may contain an additional O or S-heteroatom to form rings

There is a preference for 1-[(ndol-3-yl)carbonyl]piperazine derivatives of formula I whereir. R₂ is H and E₁ is a cyclopentyl or a cyclobexyl group.

More preferred are the compounds of formula i vinerein in addition B represents (C₁₋₄)a kyloxy or halogen, while even more preferred are the 1-(indol-3-yl)carbonyl]-plperazine derivatives of the invertion wherein B represents a mathoxy group at the 7-position of the indole ring.

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such as a morpholine, a piperazina, a homopiperazine, an imidazolidine or a

tetrahydrothiazole ring.

10 Especially preferred are the 1-{(ndol-3-y/) carbor y|piperazine derivatives of formula I wherein Ra, R1, R4, R5, R6, and R5, are H; R4, R6 and R7 are Independently H or (C1-4) alkyl; or R6 forms togetiner with R7 a 5- or 3-membered saturated heterocyclic ring and R4 is H or (C1-4) alkyl.

Particular preferred CB-1 receptor agonists of the invention are:

15 1-[[1-{cyclohexy/methy}-7-ir.ethoxy-1H-indek-3-yi]carbonyl}-8,5-dimethyl-4-ethylpperazine;

1-{!`--{cyclohexylmethyl}-7-methoxy-1 H-Indol-3-yl]carocnyl}-3,4 5-tr.methyl;lperazine; (\$}-1-{[1-{cyclohexylmathyl}-7-methoxy-1 H-indol-3-yl]carbonyl}-3,4-dimethylpiperazine;

20 (S)-2-[[1-(cyc)ohexylmethy')-7-methoxy-1/H-indol-5-yljcarborryl]-octahydro-2/H-pyrido-2/H-pyrido[1,2-a]pyrazine;

(S)-2-[[1-(cyclohexylmethyl)-7-methoxy-1ff-indol-3-yl]carbonyl]-octahydro-2ff-pyrrotc-[_,2-a]pyrazine; and (5)-2-{[1-(cyclopentyln:ethyl)-7-methoxy-1H-indol-3-yl]carbonyl}-actatrydro-2H-pyrida-25 [1,2-e]byrazine; or pharmaceutica ly acceptable satis thereof.

The '-[(indol-3-yi)carbony]piperazine derivatives of the Invention may be prepared by methods known in the art of organic chemistry in general. More specifically such compounds can be prepared using procedures outlined by C. J. Swaln et al. (J. Med. 30 Atom. 34, 140-151, 1991) and by P. E. Pererson, J. P. Wolf II and C. Niemann (J. Crg. Chem. 23, 303-304, 1968) or by modification of these procedures

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Formuta III

Formula II

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-{(Indor-3-ylicarbony))piperazines of Formula I can for instance be prepared from the condensation of a compound of Formula II, wherein R₁, R₂ and R have the meaning as previously defined and C(O)X represents a carboxylic acid or an activated derivative thereof, such as a carboxylic acid helide, preferably a choride or a bronride, with a compound of Formula III where R₂ - R₁ have the meaning as previously defined. When C(O)X represents a carboxylic acid (Le., X is hydroxy) the condensation reaction can be effected with the aid of a coupling reagent, such as for example carboryl ditridazole, dicyclohexylcarocdimide and the like, in a solvent such as dimethylicimarnide or dichloromethane.

When C(O)X represerts a cart-oxylic acid halide (i.e., X is halide) the condensation with the amine derivative III can be carried out in the presence of a base, for example interhylamine, in a solvert such as dichloromethane.

Compourds of formula III car be obtained from commercial sources, prepared by literature procedures or modifications of literature procedures grown to those parsons skilled in the art. For example, compounds of formula III can be prepared by reduction of a diketop perazine, using a reducing agent such as lithium aluminium hydride or borane-tetrahydrofuran complex as described by M. E. Jung and J. C. Rohkoff (J. Crg. Chem. 30, 4909-4913, 1985). Diketopiperazines can be prepared by a variety of routes, as described by C. J. Dinsmore and D. C. Bershore (Tetrahedron 58, 3297-3312, 2002).

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Compounds of formula II can be prepared by reaction of a compound of formula IV, where R has the meaning as previously defined, and a compound of formula V, where R and R have the meanings as previously defined and Y is a leaving group, for example a halide or an alky sulforate, in the presence of a base such as sodium hydride. The carboxylic acid can be converted to a carboxylic acid call desired, for example a carboxylic acid chloride, using a reagent such as oxalyl chloride.

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Formula V

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Compounds of formula V can be obtained from commercial sources, prepared by literature procedures or modifications of literature procedures known to those persons skilled in the art.

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For example, compounds of tormula V where Y is para-toluenesulfonete can be prepared irom compounds of formula V where Y is hydroxyl using a method described by B. Tórók et at (J. Cham. Soc. Perkin Trans. 1, 801-804, 1993). Compounds of formula V where Y is hydroxyl and R_c is hydrogen can be prepared by reduction of a carboxylic acid or carboxylic ester, using a reducing agent such as borane-tetrahydrofuran complex or lithium aluminium hydride.

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Compounds of formula IV can be accessed from compounds of formula VI by acyation at the 3-position, using an acyating reagent. For example, compounds of formula IV can be accessed from compounds of formula VI by treatment with trifluoroacetic anyhydride in a solvent such as dimethyllormarricle, followed by hydrolysis in equecus sodium hydroxice at an elevated temperature.

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Formula VI

Formula VII

Compounds of formula VI can be obtained from commercial sources, prepared by literature procedures or modifications of Itarature procedures known to those persons skilled in the art.

Compounds of formula I can alternatively be prepared by acylation of a compound of formula VII, using an acylating reagent. For example, compounds of formula II where X is chloride can be prepared by reaction of a compound of formula VII with oxalyl chloride in a solvent such as 1,1,2,2-tetrachloroethane followed by rearrangement at eleveted temperature.

Corripounds of formula VII can be prepared by reaction of a compound of formula VI with a compound of formula VI in the preserve of a base such a society hydride.

The skilled person will likewise appreciate that various 1-[(indol-3-yl);carbonyl]. Prenazine derivatives of Formula I can be obtained by appropriate conversion reactions of functional groups corresponding to certain of the substituents R and R.-R. For example, compounds of formula I wherein R, is (C₁₋₄)alcyl or (C₂₋₂)cycloalcyl, the alkyl groups of which may be substituted with OF, halogen or (C₁₋₄)alkyloxy, can be prepared by the reaction of a compound of formula, wherein Fy is hydrogen with a (C₁₋₄)a kyl relief or a functionalise (C₁₋₄)alkyl natide, in the presence of a base such as potassium carbonate.

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Compounds of formula f wherein R is (C_{1.4})alkylaxy or functionalised (C_{1.4})alkyloxy may be prepared by the reaction of a compound of formula i wherein R is hydroxy with a (C_{1.4})alkyl halide or a functionalised (C_{1.4})alkyl halide, in the presence of a base such as socium hydride.

Compcunds of formula I where in R is NH, may be prepared by the reaction of a compound of formula I wherein R is nitro with a reducing egent such as hydrogen / palladium on activated carbor.

The 1-{(indcl-3-yi)carbony!]piperazine derivatives of Formula I and their salts may contain at least one centre of chirality, and exist therefore as stereoisomers, including emanticmers and classrandomers. The present invention includes the afterementioned stereoisomers within its scope and each of the inclividual R and S enantiomers of the compounds of formula I and their sats, substantially free, i.e. associated with less than 5%, preferably less than 2%, in particular ess than 1% of the other enantiomer and mixtures of such enant omers in any proportions including the recemic mixtures containing substantially equal amounts of the two enantiomers.

Methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, e.g. synthesis with chiral induction or starting from chiral infermediates, enanticselective enzymatic conversions, separation of stereoisomers or enantioners using chiraratography on chiral media. Such methods are for example described in *Chirality in Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crooby, 1992; John Wiley).

Pharmaceutically acceptable salts may be obtained by reating a free base of a compound of formula I with a minera acid such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid, or an organic acid such as for example

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and the like.

The compounds of the invention may exist in unsolvated as well as in solvated forms with pharmacautically acceptable solvents auch as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the invention.

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ascorbic acid, citric acic, tarbaric acid, lactic acid, mafelc acic, malonic acid, 'umaric

acd, glycolic acid, succinic acld, cropionic acid, acetic acid, methana sufforle acid,

10 The present invention further provides pharmaceutical compositions comprising a 1[{ ndol-3-yl}) carbonyl] picerazine derivative raving the general formula l, or a pharmaceutically acceptable sat thereal, in admixture with pharmaceutically acceptable aux laries, and optionally other therapeutic agents. The term "acceptable" means being compatible with the other irgnedients of the corrosition and not deletarious to the recipients thereof. Compositions include e.g. those suitable for oral, sub ingual, subcutaneous, intravenous, epidural, intrathecal, intramuscular, transdermal, pulmonary, local, or rectal acrimistration, and the like, all in unit dosage forms for administration.

For oral administration, the active ngredient may be presented as discrete units, such as tablets, capsules, poxiders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invarition may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (tyophitzed) condition requiring only the addition of steriles I quid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable audilaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remirgton: The Science and Practice of Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pits, tablets, or be processed into passules, suppositionies or patches. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, enulsion, or as a spray, e.g. a rasa spray.

For maxing solid dosage units, the use of conventional acditives such as filters, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agen: of the

lose derivatives and the like, or mixtures thereof, used in suitable amounts. For parerteral administration, aqueous suspensions, isotonic saline solutions and sterile injectables solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol. The invention further includes a pharmaceutical composition, as nereinbelore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

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invention can be administered as soild compositions include actose, starch, cellu-

The 1-{(indo-13-yt})carbo-ryficiperazine derivatives of the invention were found to be agorists of the CB-1 receptor, as determined in a human CB-1 reporter assay using CHO cells. Methods to determine receptor binding as well as in vitro biological activity of cannabinoid receptor modulators are well known in the art. In general activity of cannabinoid receptor modulators are well known in the art. In general expressed receptor is contacted with the compound to be tested and binding or stimulation or inhibition of a functional response is measured.

our number of intribution of a functional response is measured.

To measure a functional response isolated DNA encoding the CB1 receptor gene, preferably the human receptor, is expressed in suitable rost cells. Such a cell might be the Chinese Hamster Cvary cell, but other cells are also suitable. Preferably the

20 cells are of mammalian origin.

Methods to construct recombinant CB1 expressing cell I nes are well known in the art (Sambrook et al., Molecular Cloning: a Laboratory Manual, Cold Spring Harbor Laboratory Press. Cold Spring Harbor, latest edition). Expression of the receptor is attained by expression of the DNA encoding the desired protein. Techniques for

Itgation of additional sequences and construction of autable expression systems are all, by now, well 'dnowr in the art. Portions or all of the DNA encoding the desireo protein can be constructed synthetically using standard solid phase techniques, preferably to include restriction sites for ease of ligation. Suitable control elements for transcription and translation of the included coding sequence can be provided to the DNA coding sequences. As is well known, expression systems are now available with a wide variety of hosts, including prokaryotic nosts such as bacteria and eukaryotic hosts such as yeas;, plant cells, insect cells, marmalian cells avian cells and the like.

Cells expressing the receptor are then contacted with the test compound to observe 55 binding, or ethmulation or inhibition of a functional response

binding, or et mulation or innibulion of a functional response. A ternat vely isolated cell membranes containing the expressed CB1 (or CB2) receptor may be used to measure binding of compound. be used. The most widely used radiolebelled cannabinoid grobe is [³HjCP=55940, which has approx mately equal affinity for CB1 and CB2 binding sites.

Another assay involves screening for cannabinoid CB1 agonist compounds by determining the second messenger response, such as for example measurment of receptor mediated changes in cAMP or MAPkinase pathways. Thus, such a method involves expression of the CB1 receptor on the cell sufface of a host cell and exposing the cell for the rest compound. The second messenger response is than measured. The level of second messenger will be reduced or increased, depending on the effect of the test compound upon binding to the receptor.

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For measurement of binding radioactively or fluorescently labeled compounds may

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In addition to direct measurement of e.g. cAMP levels in the exposed cell. cells can be used which in addition to transfection with receptor encoding DNA are also transfected with a second DNA encoding a reporter gene the expression of which correlates with receptor activation. In general, reporter gene expression of which correlates with receptor activation. In general, reporter gene expression might be controlled by any response element reacting to changing levels ofsecond messenger. Suitable reporter genes are e.g. LacZ, alkalire phosphatase, frefly fubilitiense and green fluorescence protein. The principles of such transact vation assays are well known in the art and are described e.g. in Stratowa, Ch. Hinmler, A and Czernilotsky, A.P., Curr.Opin. Biotechnol. 6, 574 (1995). For selecting active agenist compounds or the CB1 receptor the ECs, value must be < 10° M, preferably < 10° M.

The compounds may be used in the treatment of pain such as for exempte pertoperative pain, chronic pain, neuropartic pain, cancer pain and pain and spasticity associated with multiple solerosis.

25 Cannabinoid agenists of the invention would also potentially be useful in the treatment of other disorders including multipe aderosis, spasticity, infamination, glaucina, nausea and emasis, loss of appetite, sleep distributions, respiratory disorders, elergies, epilepsy, migraine, cardiovascular disorders, neurodegenerative disorders, enxiety, traumatic brain injury and stroke.

30 The compounds could also be used in conjunction with other analgesic drugs such as opicids and non-sieroldal anti-Inflammatory drugs (NSAIDs), Including COX-2 selective inhibitors.

The compounds of the invention may be administered for humans in a sufficient amount and for a sufficient amount of time to elleviste the symptoms. Il ustratively, daily desage levels for humans can be in the range of 0.001-50 mg per kg body weight, preferably in a daily desage of 0.01-20 mg per kg body weight.

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The Invention is illustrated by the following Examples.

Ехапріе 1

1-ff1-'Octonexylmethy'-7-methary-1H-rdol-3-ylcarbonyl-4-ethylpiperazine, malaic Ŋ

mixture was stirted at room temperature for 1 h, then poured into water (200 ml). The ்o a solution of 7-methaxyincole (3.5 g, 23.8 mmol) in dimethylformamide (35 m) at PC was added triffuorcacetic antryclide (4.4 ml, 31.5 mmo) over 5 minutes. The resuting 7-methoxy-3-{(trifluoromethy)carbonyljindole preopitate was filtered off, washing with water and used directly in the next step.

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heated to reflux with stirring for 1.1. The mixture was cooled and weshed twice with dietnyl ether. The aquecius phase was then ecidified to pH 1 using 5 M hydrochloric acid and the resulting line precip tate filtered off, washed with water and dried to he damp solid was suspended in 4 M sodium hydrox de so ution (143 ml) and

efford 7-met noxyIndole-3-carbox/iic acid (3.6 g). ₹

7-Methoxylndole-3-carboxylic acid (3.0 g. 16.6 mmo.) was added portionwise to a stirred suspension of sodium hydide (60% dispersion in m.neral cil, 1.56 g. 3Crrmcl) in dimethylicm amide (75 ml). After 1 h, bromomethyloycich exane (5.7 g, 32.3 mmol) ଷ

ilitered off. The crude product was recrystalised from ethyl acetate to afford 1was acced. The inxture was regied to 60°C with stirring for 1 h. The mixture was dit took with water (250 m) and washed with ethyl acetate and then diethyl ether. The squeous phase was aciditied to pH 1 using 5 M hydrochloric acid and the precipitate cyclohexylm.ethyl)-7-methoxyindde-3-carboxylic acid (3.75 g) as a crystaline solid.

To a solution of 1-(cyclohexylme:hyl)-7-methoxyindale-8-carboxylic acid (2.5 g, 8.8 mmol) ir THF (30 mi) was addec oxalyl chloride (4.5 g, 85.3 mmo.), dropwise with The mixture was stirred at room temperature for 18 h. The volatile components were evaporated under reduced pressure to afford 1-(cyclohexy/methyl)-?-melhoxyindole-3-carbonyl chloiide (2.7 g) as a crystalline solid. string. 었

To 1-(c/clohexylmethy). 7-methoxyindcle-3-carocnyl.chloride (* . 9 g., 6.2 r-mal) was added a solution of Akethylpiperezine (1.35 g, 11.8 mmol) in dichloremethane (60 mli. The mixture was stirred until the acid chloride dissolved. Triethylamine (3 ml, 21.5 mmol was acded and the solution stimed at room temperature for 16 h. The eaction mixture was washed with water (2 \times 50 ml), dried with socium sulfate and evaporated to afford an oil. This was purified by flash chromatography eluting with 0-10% (VV) methanol in dich oromethane to afford the title compound (free base) as a 8 8

of maleic setid (0.83 g. 7.15 mmd) n ether (24 ml) and methanol (4 ml). The resulting mixture was ettired for 30 minutes and the sold filtered off. The solid was recrystallised from methano /diethy/ ether to afford title compound (1:1 maleic acid saft) as a crystallised from methano /diethy/ ether to afford title compound (1:1 maleic acid saft) as a crystalline solid (2.7 g, 5.4 mmo). ¹H NIMR (4COMHz, CD₃CD) & 0.89-1.08 (2H m), 1.12-1.25 (3H, m), 1.36 (3H, t, J.7.5), 1.56 (2H, d, J. 12.5), 1.69-1.74 (3H, m), 1.77-1.89 (1H, m), 3.22 (2H; g, J.7.5), 3.30-3.35 (4H, m), 3.55 (3H, s), 5.80-4.05 (4H, m), 4.25 (2H, d, J.7.0), 6.25 (2H, s, maleate) 6.76 (1H, d, J.7.5), 7.10 (1H, t, J.7.5), 7.26 (1H, d, J.7.5), 7.53 (1H, s); E MS: m/z = 384.2 [M+Hf].

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The free base was dissolved in diethyl ether (50 mf) and filtered into a stirred solution

Example 2

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1-f[1-iCyclopenNimethyl)-7-methoxy-1*H*-incol-3-ylycarbonyl]-4-ethylpiperazine, hydrochlorice salt Cyclopentaneme:hanol p-tcl.zenesulfona:e was prapared by the following method: To a solution of cyclopentaneme:hanol (2.0 g, 20.0 mmol) and pyridine (2.9 ml, 36.3 mmol); in dichloromethene (20 ml) was added p-toluenesu tonyl chloride (3.46 g, 18.1 mmol). The mixture was stirred at room tamperature for 24 h under nitrogen. The resulting mixture was washed with 2M hydrochloric add and the aqueous layer separated and extracted with citchloromethane. The combined organics were cried over sodium sulphate and concentrated under reduced pressure to yield exclorementanol p-toluenesulfonate as a colouriess oil (4.3 g, 17.0 mmol).

The title compound was prepared following the method of Example 1, using cyclopentane methanol p-toluenesul onstee instead of promorpethyloydohavana. ¹H NI/R (400MHz, CD₈CD) 5_H 1.29-1.35 (2H, m), 1.38 (3-, t, J7.5), 1.52-1.71 (6H, m), 2.39-2.49 (1H, m), 3.24 (2H, c, J7.5), 3.05-3.35 (2H, br mi, 3.35-3.70 (4H, br m), 3.85 (3H, s), 4.38 (2H, d, J7.5), 4.40-4.65 (2H, br m), 6.79 (1H, d, J7.5), 7.10 (1H, t, J7.5), 7.60 (1H, s), EIMS: m/z = 370.2 [M+H]⁺.

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Example 3

35 The procedure described under Examples 1 and 2 was further used to prepare the following compounds:
3A: 1-if1-(c/c)ohapt/imethylp-7-methoxy-1H4ndol-3-yllcarbonyl-4-ethylpiperazine,

<u>hydrochloride salt</u> was prepared using cycloheptar.emethanol p-tol Jenesultonate.

EIMS: m/z = 398.2 [M+H⁻¹

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38: 1-II14(Cyclooctylmethyl)-7-methcyy-1H-indol-3-yllcarboryll-4-e-thyloperazine, mydrochlorida salf was prepared using cyclooctanemethanicl p-toluenesyllonate EIMS: m/z = 412.4 [M+H].

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3C: 1-[1-4Cyclohexylmethyl) -7-methoxy-1H-Incol-3-/Ilcarbonyl]-4-(2-

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hycroxyethy)piperazine, trifluoroacetic acid sal: was prepered following the method of Example 1, using 1-{2-hydroxyethy!)piperazine instead of A-ethypiperazine, EMS: m/2 = 4C0.2 "V-HI".

3D: 1-i[1-(Cyclchexylmethyl)-7-methoxy-1H-indol-3-y loarbonyl-4-[2-methoxyethyl)piperazine, trifluoroacetic acid sa t was prepa ed using 1-(2-

methoxyet-nylptperazine. EIMS: m/z = 414.2 [t/+H]*.

3E: 1-[[1-(Cyclohexy/methyl)-7-methyl-1H-incloh-3-yl]:zart-onyl)-4-et-nylo-perazine was obtained tollowing the method of Example 1, using 7-methy inclohe instead of 7-methycyindole. EIMS: m/z = 388.0 [M+H-]*.

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3F: 1-{[1-iOxclohexyl=ethyli-7-ethyl-1 H-indol-3-yl]carbony}-4-ethylpipe:azine was 15 obtained from 7-ethylindole. EINS: m/z = 38.2.2 [M+H]*.

Example 4

1-[[1-iCyclohexylmethy],-5-fluoro-1 //-indol-3-yllcarbonyl]-4-e.hylpicerazine, hydrochloride satt

To a solution of 5-fluoro indole (1.0 g, 7.4 mmcl) in dimethyl formamide (20 ml) was added sodium hydride (60% dispersion in mineral oli; 327 mg, 8.14 mmol). The mixture was stirred at room temperature for 10 minutes before the addition of bromomethyloyclohexane (1.3 ml 9.3 mmol). The resulting mixture was stirred at room temperature for 15 hours. A further addition of sodium hydride (170 mg, 4.23 mmol), then promomethyloyclohexane (0.65 ml, 4.65 mmol) was made and the reaction sirred for a further 15 hours.

The reaction was quenched with 2-propanol (10 ml) and then concentrated. The resulting brown gum was partitioned between ethyl acetate (50 ml) and 5% sodium hydrogen carochate solution (50 ml). The organic layer was washed with water (50 m), dried over sodium suitate and concentrated. The crude intermediate was then purified by flash chromatograp by using 95% dichloromethane, 5% methanol as eluent, to a ford 1-(cyclohexylmethyl)-5-fluoroindole (1.25g, 5.45 mmol).

To a solution of 1-(cyclohexylmethyli-5-fluorondole (208mg, 0.5 mmol) in 1,12,2-elrachloroethane (15 m) at 0°C, was added oxalyl chloride (0.122 m), 0.945 mmol) with stirring under a stream of nitrogen. The mixture was allowed to warm to room temperature over 1 hour, then reated to 120°C for a further 1.5 nours. The mixture

hours and then partitionac between 0.4 M sodium hydroxide so ution (10 ml) and [학 15 Stirring was continued for a further 10 minutes before the addition of Methylptiped chicromethane (10ml). The organic layer was washed with water (10 ml), dried over Na₂SO₄ and concentrated. The resulting brown oil was purified by flash chromatoas eluent to yied the nazine (0.125ml, 0.99mmol). The mixture was stirred at room temperature graphy using 95% dichlorcartethane, 5% methanol compound as the free base.

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tydrochloride sell formation was achieved by the addition of hydrogen chloride 2M solution in diethyl ether (3 mi) to a solution of the free base in diethyl ether (5 ml). The precipitate was filtered and orled. The solid was crystallised from diethyl ether and methanol to afford title compound (1:1 hydrocitoric aclc salt) as a crystalline solid (0.172 g, 0.42 mmol). 14 NMR (400MHz, CD₃OD) & 0.98-1.27 (2-1, mj, 1.1?-1.27 (3H, m), 1.39 (3H, 1, J 7.5), 1.59 (2H, d, J 13.0), 1.64-1.77 (3H, m), 1.89-1.83 (1H, 1T), 3.08-3.20 (2H, 1T), 3.24-3.32 (2H, 1T), 3.51 (2H, 1; 1J 12.5), 3.63 (2H, 1C, 1J 11.0), 4.07 (2H, d, J7.5), 4.58 (2H, d J 12.5), 7.04 (1H, 1d, J 9.0, 2.5) 7.45 (1H, dc, /8.5, 2.5), 7.47-7.51 (1H, mj, 7.77 (1H, s); E MS: miz = 372.0 [MHH]

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Example 5

The procedure described uncer Example 4 was further used to prepare the following compounds: g

5B: 1-{[1-(Cyclohexylmethyl)-7-fluoro-11-indol-3-yl]carboryl--4-ethylciperazine 5A: 1-fff: (Cyclohexylmethyl)-6-fluoro-1.H-.ndol-3-yl)carbom/l-4-ethylciperazine. hyd:ochloride sal: was obtained from 6-fluorchdole. EIMS mtz = 372.0 [M+H]*

5C: 1-{[6-Brono-1-icyclohexylmethyl}-1H-indol-3-v|]carocnyl}-4-ethylpiperazine :ydroch orige salt was obta ned from 6-bromoindole. EIMS: m/z = 432,4 [M+H]* 5D: 1-[[7-Bromo-1-(cyclohexy/methyl)-1/f-indol-3-yllcarbonyll-4-ethylpiperazine nydrochloride salt was obtained from 7-bro-noindale. EIMS: mz = 452.5 [M-4]* hydrochlorida sal: was obtained from 7-fluoreindole. EIMS: m/z = 372.0 [M4H]* 33

5Ε: 1-[[5-C τιο το -1-(cyclohexv/methy])- : Hindcl-3-yillcarbony]-4-ethylpiperazire. 5F: 1-([6-Chloro-*-(cyclohexymethyli-1/f-indxi-3-yilcarbonyl]-4-ethybioerazine, 5G: 1-[[7-Chloro-1-(cyclohexvimethyl)-1 H-Indol-3-yllcarbonyl}-4-ethylpiperazine hydrochloride salt was obtained from 5-chloroIndole. EIMS: m/z = 396.2 M+H] hydrochloride saft was obtained from 6-ch oroindole. EIMS: $m/z = 398.5 \text{ M+H}^{-}$ \underline{w} drochlonde salt was obtained from 7-chloroindole. EIMS: m/z = 338.0 [M+H]⁻ 8

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wes cooled to room temperature and triethylamine (0.138ml, 0.99mmol) was added.

hydrochloride saft was obtained from 6-cyanoindole. EIMS: m/z = 379.4 [M+H]*.

51: 1-[[1-(1-Cyclohexylettyl)-1H-indol-3-y][carboryl]-4-eIhybiperazing, hydrochioride saft was obtained from indole and racemic i-cyclohexyl-1-p-toluenes.ultonyl ethane.

EIVS m/z = 568.0 [M+H]*.

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5H: 1-il3-Cvano-1-(crclohaxylmethyl)-1H-indol-3-yllcarbonyll-4-ethyloiperazine

The product obtained in Example 51 was subjected to china. HPLC separation on a Chirace. OD column (2 cm x 25 cm), eluting with sohexane/sopropanol 95/5 (v/v) at 20 m/min flow rate. The products were cetected using a UV detector at a wavelength of 240nm.

10 (-)-51: Enentiomer 1; retention time 8.1 minutes; enantiomeric excess >98%, [3]0²² -12° (c=1.25 rng/ml n CHCt₃).

(4)-51: Enantiomer 2 retention time '1.1 minutes; enantlomeric excess > 98%, $[a]_0^{22} + 7^{\circ}$ (c = 1.50 mg/ml in CHCl₃).

5<u>J: 1-f[1-{1-Cyclohex/dethyl}-6-methoxy-f.H-indol-3-yltrarbonyl}-4-ethylpiperazine,</u>
15 <u>fydroch'ori3e salf</u> was obta ned from 6-methoxyindale and 1-cyclohexy -1-ptoluenesulforyl ethane. ElMS: m/z = 398.2 [M+H⁻¹.

5K: 1-[[1-(1-Cyclohaxylethyl]-7-methoxy-1/Hindol-3-v]carbonyl]-4-ethybiperazine, hydrochloride saft was obtained from 7-methoxylndole and 1-cyclohexyl-1-p-toluenesulfonyl ethane. E MS: m/z = 398.2 [M+H]*.

50 51.: 1-[11-(Ovclohexylmethyl)-6-n.tro-1*H*-indol-3-yllcarbonyl)-4-ethylpiperazine, hydrochloride sall was ob:ained from 6-n troindole. EIMS: m/z = 399.2 [M+H]*.

5M: '-{[1-(Cyclohexylmethyl)-7-niro-1*H*-indol-S-yl carbonyl-4-ethylpiperazine, hydrochloride sall was obtained from 7-nitroindole. EIMS: m/z = 399.2 [M+H]*

5N: 1-[17-Berzyloxy-1-(cyclonexylmethyl)-1*H*-Indol-3-ylicarbonyl-4-ethylpiperazine,

25 <u>hydrochbrida salt</u> was obtaired from 7-berzyloxylndola. EIMS: m/z = 460.4 [M+H].

50: 1-(1-10/2) obexylme:hyl)-6-methoxy-14-hidot-3-viberbonyl-4-ethyloiparazine,
ma'eic acid salt was obtained from 6-methoxylrdo:e. EIMS: m/z = 334.5 [M+H]*.

5P: 1-(11-(2)/Cbhexylmethyl)-7-methoxy-14-inclose-3-vilcarbonyl-4-

isopropylpiperazine, hydroch oride salt was obtained from 7-methoxylndole and 1-30 isopropylpiperazine, EIMS: m/z = 398.2 [M+H][‡]
50: 1-[11-(Cyclohex-3-enylneihy)-7-methoxy-1H-indol-3-ylcarbonyl-4-

 $\overline{\mathrm{e}.\mathrm{h}/\mathrm{piperezire}}$ was obtained from 7-methoxyindole and cyclotiex-3-enemethanol p-

ioluenes. If on at $\pi / \lambda = 392.2 [M+H]^{-}$.

hydrochloride selt was colained using S-fluoraindale and Manethyt pipotazino. EllaS. 5S: 1-{1-{Cycloheavylmethyd}-5-fluoro-1 H-indol-3-ylloarbonyl}-4-methylpiperazine, m/z = 358.2 [M+H]*

hydrochloride selt was obtained from 6-fluorcindole and M-methyl piperazine. EIMS: 5T: 1-{11-{Cyclohexylmethyl}-6-{lucrc-1*H*-indol-3-ylkarbonyl}-4-methylpherazine. TH+WI 0.85E = 3/H

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hydrochloride salt was obtained from 7-fluoroindole and M-methyl piperazine. EIMS: 6U: 1-[i1-(Cyclobaxytmethyl)-7-fluoro-11-indol-2-yl carbonyl-4-methylpiperazine, m/z = \$58 0 [M+H]*.

hydrochloride sall was obtained from 6-chloror dole and A-methyl piperazine. EIMS: 5V: 1-JIG-Chloro-1-jcyclohexylir ethyl)-1 H-indol-3-wllcarborryl}-4-methylci perazine, 2

ydroch onde sell was obtained from 7-chloroir doe and N-methy piperazine. EIMS: 5W: 1-[[7-Chore-1-(cyclohexylmefhyl)-1H-tdo-3-yl carbonyl)-4-nethylpiperaz.ne. $m'_2 = 374.2 \{ NHH \}^2$ 5

hydrochloride salt was obtained from 6-cyanoincole and M-methylpiperazine. EIUS: 5X: 1-{/6-Cyano-1-{cyclohexylmethyl}-1 H-indol-3-yllcarbonyl}-4-methylpiperazine, $\pi t_2 = 365.0 \text{ [M+H]}^2$.

hydrochloride salt was obtained from indole, N-methylpiperazine and 1-cyclohexyl-1-5Y: 1-III-(1-Cyclohexylethyll-6-methoxy-1H-indol-3-y]carbonyll-4-methylpiperaz ne, hydrochloride sail was obtained from 6-methoxyindole. N-methyloiperazine and 1-52: 1-[[1-(1-Cyclohexylpropy]-1H-indol-3-yl]carbony]-4-methylpperazine cyclohexyl-1-p-toluenesulfonyl ethane EIMS: $m/z = 364.2 [M-H]^+$. c-toluenesculforly propare. EIMS: $m/z = 368.0 \text{ [M+H]}^+$. প্ত

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Example 6

mixture was stirred at room temperature under hydrogen for 15 hours after which it (200 mg. 0.5 mmol) was cissolved in methanol (10ml) to which was added palladium (5 wt. % on activated carbor; 50mg, cat.) as a stury in methanol (3ml). The system was then sected and flushed with nitrogen before fixing a hydrogen source (balloon). The was filtered through celite and concentrated. The resulting brown oil was purified by lash chromatography using 95% dich oromethane, 5% methanol as eluent to yield 1.12 (3H, 1, J.7.5), 1.17-1.26 (3H, m), 1.53 (2H, d, J.12.5), 1.63-1.75 (3H, m), 1.87-1.98 (11, m), 2.44-2.55 (6H, m), 3.37 (4H, t, J.5.0), 4.20 (2H, J. J.7.5), 6.59 (1H, dd, the title product as the free base. ¹H NMR (400MHz, CJ₂OD) 4, 0.97-1.08 (2H, m), 1-{[7-Amino-1-(cyclohexylmethyl)-1 /4-indol-3-ylcarbonyl-4-ethylpiperazine 4-[[1-(Cyclchex/rrefhyl)-7-nitro-1/Hndol-3-yi]carbonyl}-1-ethylpiperazine 띪

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J7.5; 1.0), 6.93 (1Н , 1, J7.5), 7.06 (1Н, dd, J8.0, 1.0), 7.39 (1Н, sj; EIMS: m.z 389.0 [k/+H]*.

Example 7

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1-(T-(Cyclohexy.methyt)-7-hydroxy-1.H4ncol-3-yfloarbony 1-4-ethyfoiperazine, bydrochlaride salt

To a solution of 4-{[7-barzylaxy-1-(cyclohexytmethyl]-1/H-indole-3-yl]carbanyl}-1-ethytriperazine (1 g 2.2 mmol) in ethanol (50m), was added paliadium (5 wt. % on activated carbon; 100 mg). The mixture was hydrogenated under a pressure of 5.5 bar at 60°C for 16 hours. The resulting mixture was filtered through dicalite, and the filtrate concentrated under reduced pressure to afford the title compound (free base) as a gum (865 mg, 2.3mmol).

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Hydrochlaride sail formation was achieved by the addition of hydrogen chloride (2th solution in delity) either, Sml; to a solution of the free base (180 mg, C.5mmd); in diethyl either, Sml; to a solution of the free base (180 mg, C.5mmd); in diethyl either (5 ml). The precipitate was filtered and dried. The solid was crystallised from diethyl either and eithand to afford the title compound (1:1 hydrochloric acid salt) as a crystalline solid (132 mg, 0.3 mmol). 1 NMR (400MHz, CD₃OD) &₁₁.05 (2H, m), 1.38 (3H, t, J.7.5;, 1.57 (2H, m), 1.69 (3H, m), 1.92 (1H, m), 3.13 (2H, m), 3.27 (2H, q, J.7.5;, 3.45 (2H, m), 3.61 (2H, d, J.12.0), 4.29 (2H, d, J.7.0), 7.52 (2H, d, J.14.2), 6.59 (1H, d, J.7.0), 6.57 (1H, 1, J.7.0), 7.14 (1H, d, J.7.0), 7.52 (1H, si; ElMS: m/z = 370.2 PM+Hf*.

Example 8

1-![1-{Cyclohex.drrethyth-7-(2-fluoroethoxy)-1.H-hool-3-y.]:arbony-1-4-ethylpperaz.ne eluent to afford the title compound (54 mg, 0.1 mms),. ¹H NMR (400MHz, CD₈CD) $\delta_{\rm H}$ was purified by flash chromatography using 95% dichloromethane, 5% methanic as The resulting prown gum was partitioned between dichloremethane (50 ml) and 5% 1.C5 (2H, n), 1.19 (3H, m), 1.39 (3H, t, J.7.5), 1.56 (2H, m), 1.69 (3H m), 1.92 (1H, 0.54 mmol) in d'methylio:rramide (5.n.). After 30 mhutes, 1-bromo-2-fluorcefhane (49 µl, 0.65 mmol) was adoed. The mixture was heated to 60°C with stiming for 48 water (50 ml), dried over sodium suficte and concentrated. The crude intermediate cyclohexylmethyl)-7-hydroxy-1*H*-fr.do.e-3-yl]ca-bonyl}-1-ethylpiperazins (200 mg, hours. The readion was quenched with 2-propanol (10 ml) and then concentrated. sodium hydrogen cart onate solution (50 ml). The organic layer was washed with Sodium hyoride (60% dispersion in mineral oil, 55 mg, 1.52 mmcl) was added portionwise with starting under a stream of nitrogen to a solution of 4-4(1ß ස 33

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m), 2.48 (2H, q, J7.0), 2.53 (4H, m), 3.75 (4F, t, J5.0), 4.26 (2H, d, J7.5), 4.32 (1H, m), 4.39 (1H, m), 4.75 (1F, m), 4.87 (1H, m), 6.73 (1H, d, J8.0), 7.06 (1H, t, J8.0), 7.26 (1H, t, J8.0), 7.44 (1H, s); EIMS: m/z = 416.2 [M+H]*.

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Example 9

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1-([1-(Oxtohexymethyli-7-etf.oxy-1-Hindol-3-vi]carocnyli-4-ethylpiperazine was prepared following the procedure described under example 8, using bromosthane instead of 1-bromo-2-flucroethane. EliMS: miz = 398.2 [M+H]*.

10 Example 10

1-{11-;Cyclohexylmethyli-7-methoxy-1,H-indol-3-yllcarbonyll-2,3,5,6-

letramethy piperazine, nydrochloride sall

To a solution of disoprocylethylamine (0.83 ml, 4.90 mmol) and 2.3,56tetramethy piperazine (0.35 g, 2.45 mmol) in dichteremethane (5 ml) was added a

15 so ution of 1-(cyclohexylmethyl)-7-methoxylmclole-3-carbonyl chloride (0.33 g, 1.09 mmol, prepared following the method in Example 1) in dichtoromethane (5 ml). The mixture was stirred at room temperature for 8 h, evaporated under reduced pressure and the residue purified by flash chromatography eluting with 5-10 % (v/v) methanol in dichloromethane to afford the 11.9 compound (free base) as a colourless oil (0.43).

dropwise with 2 M hydrochloric acid in diethyl ether (3.3 ml) and diethyl ether (3 ml), treeted dropwise with 2 M hydrochloric acid in diethyl ether (3.3 ml) and diethyl ether (3 ml).

The resulting precipitate was collected by filtration, weshed with diethyl ether (15 ml) and dried under reduced pressure to afford the title compound (1:f hydrochloric acid satt) as a white solid (0.09 g, 0.20 mmo). TH NMR (400MHz, CD₃OD) & 0.396-1.39 (3H ml), 1.42 (6H, d, J7.0), 1.64-1.89 (9H, ml), 3.44-5.70 (3H, ml), 3.95 (3H, s), 4.21-4.34 (3H ml), 6.77 (1H, d, J7.7), 7.11 (1H, 1, J6.2), 7.38 (1H, d, J8.2), 7.58 (1H, s);

Example 11

EIMS: n/2 412.4 [NI4H]*.

30 1-f[1-fCyclohexylmethyll-7-meth.xy-1H-indol-3-yllcarbonyli-2,6-cimethy piperazine, hydrochloride salt

4-[[1-(Cyclohexylmethyl)-7-methoxy-1H-hdol-5-yl]carbo nyf.-3,5-cimethyplperazine-1-carboxy is acid terf-buryl ester was prepared folkwing the method 1n Example 10 using 3,5-dimethylpiperazine-1-carboxylic acid terf-buryl ester (E. J. Jacobsen et af, J. Med. Chem. 42, 1123-1144, 1999) inscead of 2,3,5,5-teramethylpiperazine. To an ios cooled solution of 4-[[1-(cyclohexylmethyl)-7-methoxy-1H-indol-3-yl]carbornyl]-3,5-dimethylpiperazine-1-carboxylic acid terf-buryl ester (C.52 g, 1.08 mmol) in

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dichloromethane (5 ml) was added dropwise influoroacetic acid (2 ml). The mix.ure

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was allowed to warm to room temperature over 2 h before removal of any vicially components under reduced pressure. The residue was then suspended in 5 M socium hydroxide solution (10 ml) and extracted into dichlororrethane (2 x 30 ml). The combined organic layers were dried with magnesium sulfate and evaporated to an oli. This was purified by fash chromatography eluting with 5-10 % (Wv) mathanol in dichloromethane to afford the title compound (free base) as a colourlass oil. The free base was dissolved in diethyl ether (3 ml) and treated dropwise with 2 M hydrochloric acid in clethyl ether (1 ml). The resulting precipitate was collected by filtration, washed with diethyl ether (15 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sait) as a colourless sold (0:13 g, 0:31 mmcli. The WMR (400MHz, CD₂OD) &. 1.62-1.90 (4H, mi, 3:33-3:42 (4H, m), 3:39-3:42 (4H, m), 3:39-3:42 (2H, m), 3:39-3:42 (2H, m), 3:39-3:42 (2H, m), 3:39-3:42 (2H, m), 3:39-3:42 (1H, d, J7.5), 7.46 (1H, s); EIMS: m2:384.2 [M-H].

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Ехаптре 12

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1-f[1+iQvdohexy/methyl)-7-mathoxy-1/H-ir.do!-3-yl carbonyl-3,5-3|methylploerazine hydrochloride salt

0.87 mmd, prepared following the method in Example 1) and 2.6-dimethylpiperazine dichloromethane to afford the title compound (free base) as a colourless oil. The free (0.16 ml, 1.05 mmol) and 1-hydroxycenzotriazola (0.01 g. 0.09 mmo). The mixtures was stirred at room terr perature for 18 h. The mixture was washed with 5 M sodium .36 (24, br d, J '2.0), 1.62-1.90 (4H, m), 3.06 (2H dd, J '4.5, 11.5), 3.39–3.53 (2H (0.12 g, 1.05 mmuli in dichloromether.e (10 ml) was added disopropylcarbodimide mj, 395 (3H, s), 4 26 (2H, d, J7.5), 4.52 (2H, br d, J13.5), 6.77 (1H, c, J7.5), 7.1 hydroxide (2 x 10 ml), cried with magnesium sulfate and evaporated. The residue hydrochloric acid in diethyl ether (1 ml). The resulting precipitate was collected by To a solution of 1-(cyclonexylmethy)-7-methoxy-indole-3-carboxylic acid (0.25 g. base (0.15 g) was dissolved in defry! ether (3 mi) and treated dropwise with 2 M afford the little compound (1:1 hydrochloric acid salt) as a colcurless solid (0.15 g. 6.36 mmo), 14 NMR (43CMHz CD3OD) 8,4 0.98-1.26 (5H, m) 1.32 (6H, d, J.6.5), filtration, washed with diethyl ether (15 m) and drien under reduced pressure to was purified by flash chromatography eluting with 5-10 % (viv) methanol in (1H, 1, JB.0), 7.24 (1H, d, JB.C), 7.54 (1H, s); EIMS: m/z 384.2 [M++-]* 8 S 8 35

Example 13

The procedure described under example 12 was further used to prepare the following compounds

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13A: 1-[11-(Cyclohexylmethyl)-7-methoxy-1H-indob-3-y Isarbonyl-3-methylpiperazine. carboxylic sold and rac-2-methylpiperazine. 1H NMR (400MHz, CD,GD) &, 0.98-1.24 (6H, m), 1.32 (3H, d, J.6.5), 1.56 (2H, br.d, J12.5), 1.63-1.86 (4H, m), 3.17-8.22 (2H, m), 3.39-3.51 (3H, m), 3.54 (3H s), 4.26 (2H, d, J7.0), 4.43 (2H br d. J14.3), 6.76 (1H. d, J7.5), 7.1 (1H, t, J7.5), 7.25 (1H, d, J8.0), 7.54 (1H, s). EIMS; m/z = 370.2 hydrochloride sat was prepared using 1-(cyclohexymethyl)-7-rrethoxy-indo'e-3-'n 9

13B: 1-i(1-(Cyclobentylmethyl)-7-methoxy-1*h*-ndol-3-yllcarboryl)-3-

Cinethy programe, hydroch oride sall was prepared using 1 (cyclopenty) methyl)-7methoxy-indole-3-zarboxylic acid and 2,6-dimethy/piperazine. 14 NMR (400MHz

dd, J14.5, 11.£), 3.39–3.53 (2H, m), 3.95 (3H, s), 4.37 (2H, d, J7.5), 4.52 (2H, d, J CD₃OS) δ₁ 1.24-1 36 (8H, m), 1.51-1.72 (3H, m), 2.43 (fH, heptet, J.7.5), 3.07 (2H, 14.C), 6.77 (1H. d, J.7.5), 7.10 (1H. l, J.7.5), 7.24 (1H, d, J.8.0), 7.55 (1H, s). EIMS; m2 = 370.2 [N+H]*. 5

13C: (S)-1-[(1-(C/clopartMmethyl)-7-methoxy-1H-indol-3-yl]cart-onyl+3-

dd, J 14.5, 10.9), 3.36–9 5 (3H, m), 3.95 (3H, si, 4.37 (2H, d, J 7.5), 4.43 (2H, br d, J OD₃OD) & 1.26-* 36 (EH. m), 1.51-1.72 (6H, m), 2.42 (1H, heptet, J.7.7), 3.20 (2H, 14.5); 6.77 (114, d. J7.6); 7.10 (114, t. J7.7); 7.26 (114, d. J8.1); 7.59 (114, s). EIMS; <u>meth/picerazire, hydrochloride salt</u> was prepared using 1-(cyclopentylmethy)≻7nethoxy-indole-3-carbcxyt c acid and (S)-2-methy piperazine. 1- NMR (400MHz, X

" = 356.2 [M+H] 3

130: 1-[[1-(Cyc'ohexyl'nethyl)-7-methoxy-1H4ndol-3-yllcarbonyl-3,3-

00,00j &, 1.10-1.22 (5H, m), 1.38 (6H, s), *.54-1.86 (6H, m), 3.31-3.34 (2H, m), 3.2 dimet viologerazine, hydrochloride salt was prepared using 1-(cyclohexylmethyl).?. methoxy-irdo e-3-carboxylic acid and 2,2-dimethylpiperazine. H NMR (400MHz,

(2H, dd, J14.5, 10.9), 3.81 (2H, s), 3.95 (5H, s), 3.96-3.99 (2H, n), 4.26 (2H, d, J 7.1), 6.76 (1H, d, J7.5), 7.10 (1H, t, J.8.1), 7.24 (1H, d, J.8.0), 7.53 (1H, s). EIMS; $m/z = 384.5 [M+H]^{-}$ 8

13E: (S)::-[[1-iCyclohexylmetry/]-7-methoxy:1 rl-ndol-3-v]]caroonyl]-3-methyl-

indole-3-carboxylic acid and (S)-2-mathylp perazine. ¹H NM:4 (400I/Hz, CD₆OD) S_H oloerazine, hydrochloride sall was prepared using 1-(cyclohexylmethyl)-7-methoxy-.C**123 (5H, m), 1.33 (3+, d. J&ā), 1.52-1.97 (6H, m), 3.16-3.27 (2+, m), 3.38 32

3.51 (3H, m), 3.95 (3H, s), 4.27 (2H, d, J.7.0), 4.43 (2H, br. d, J.14.3), 6.76 (1H, d, J.7.8), 7.10 (1H, t, J.7.9), 7.25 (1H, d, J.8.0), 7.54 (1H, s) EIMS; m/2 = 370.0 [M4+H]².

13F: (Ri-1-[11-(Cycloheaylmethyl)-7-methoxy-1H4hdob-3-ylcerbonyl-3-methylp.)

reflinkbiperazine, hydrochloride salt was prepared using 1-(cycloheaylmethyl)-7-methoxy-incole-3-zartoxylic acid and (Fi-2-methylp perazine, "H NMR (400MHz, CD₂OD) 5.1.101-1.23 (5H, m), 1.33 (3H, d, J.6.3), 1.52-1.67 (5H, m), 3.16-3.27 (2H, m), 3.35 (3H, s), 4.27 (2H, d, J.7.0), 4.43 (2H, br.d, J.14.3), 5.76 (1H, d, J.7.5), 7.10 (1H, t, J.7.9), 7.25 (1H, d, J.8.0), 7.54 (1H, s). EIMS: m/z = 370.0 [M4+H]².

S

5

10 Example 14

:-{[1-iCyclo texylmethyl}-Z-methoxy-1H-indoh3-yl]carbonyl}-3,5-dimethyl-4ethylpiperazins, hydrochloride salt To a solution of 1-[11-(Cyclohexytmethyl)-?-methoxy-1H-indol-8-y]carbonyi}-3,5-dimethylptperazine (0.7 g, 1.83 r-ma) and potassium carbonate (0.3 g, 2.19 mmai) in dimethylptperazine (5 ml) was added to aborthane (0.17 ml, 2.10 mmol). The mixture was heated to 50°C for *8 h and diluted with water (20 ml). The suspension was then extracted with methyl terf-bulyl ether (2 x 30 ml), the combined organic layers washed with water (3 x 20 ml), dried with magnesium sulfiate and evaporated. The residue was purified by flash of romatography eluting with 5-10 % (vv) methanic in

dict-foromethane to afforc the title compound (free base) as a colour ess of. The free base (0.42 g) was dissolved in diethyl ether (10 ml) and treated dropwise with 2 l/hydrochloric acid in diethyl ether (1 ml). The resulting precipitate was collected by filtration, washed with diethyl ether (15 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sall) as a white solid (0.35 g, 0.78 mmol). 'H NIMR (4C0MHz, CD₃OD) &, 0.98-1.23 (5H, m), 1.30 (5H, t, J7.0), 1.39 (6H, d, J7.0), 1.53-1.88 (6H, m), 3.42-3.35 (2H, m), 3.42-3.61 (4H, m), 3.95 (3H, s), 4.26 (2H, d, J7.0), 4.55 (2H, br d, J13.0), 6.77 (1H, d, J8.0), 7.10 (1H, t, J8.0), 7.27 (1H, d, J8.0), 7.57 (1H, s). EthMS: m/z 412.4 'M+HJ*.

30 Example 15

The procedure cescribed under example 14 was further used to prepare the following compounds:

15A: 1.fl1-iOxclopentylmathyl)-7-mathoxy-1H-indol-3-Allcarbonyll-3.5-dimethyl-4ethylpiperazine_hydrochloride_sall_was prepared using 1-f[1-(cyclopentylr-athyl)-7-35 rethoxy-1H-indol-5-yl_carbonyl}-3,5-dimethylpiperazine_1H NMF (430/Hz, C3_4OD) 5- 1.27-1.40 (5H, rr.), : .39 (6H, d, J6.5), 1.73-1.43 (6H, m), 2.44 (1H, hep:et, J7.C), 3.22-3.33 (2H, m), 5.42-3.61 (4H, m), 3.55 (3H, s), 4.38 (2H, d, J7.0), 4.53 (2H, br d, J14.5), 6.77 (1H, d, J8.0), 7.10 (1H, t, J8.0), 7.27 (1H, d, J8.0), 7.61 (1H, si, EIMS; m/z = 399.0 [JM+H]*.

15B: 1-[1-(Cyclohex/methyl)-7-methoxy-1 H-Indel-3-vllcarbomyl-4-ethyl-2.3.5.6-fetramethypicenazire, hycnochlorida sail was prepared using 1-[1-(cyclohexyl-methysicenazire, hycnochlorida sail was prepared using 1-[1-(cyclohexyl-methyl)-7-methoxy-1 H-indel-3-yl]carbomyll-2.3.5.6-tetramethypicenazire. H NWfR (400VHz, CD₂OD) & C.98-1.29 (8H, m), 1.32 (3H, t, J6.5), 1.44-1.88 (15H, m), 3.32-3.83 (5-H, m), 3.95 (3H, s), 4.20-4.41 (3H, m), 6.77 (1H, d, J8.0), 7.11 (1H, t, J

'n

10 15C: 1-i[1-(Cyclchex/Imethyl)-7-methoxy-11-Hindcl-3-vilcarbonyl}-2,6-dimethyl-4-efhylpparazing_hydrochloride salt was prepared using 1-i[1-(cyclohexylmethyl)-7-methoxy-1-Hindol-3-yllcarbonyl}-2,6-dimethylpperazine 1-1 NIMR (400MHz, CD₃OD) 8_H 0.37-1.22 (5-4, m), 1-43 (3H, t, J 7.0) 1.45 (6H, d, J 8.0), 1.51-1.88 (6H, m), 3.23-3.41 (4H, m), 3.55 (2H, br c, J *1.0), 3.95 (3H, s), 4.26 (2H, d, J 7.0), 4.86 (2H, br s).

8.0), 7.37 (1H, c, J8.5), 7.55 (1H, s). EIMS; 1n2 = 440.2 [W+H]*.

15 6.78 (1H, 4, 47.5), 7.1 (1H, 1, 48.0), 7.23 (1H, c, 38.0), 7.48 (1H, s). Ell/S; m² = 4'2.4 [M+H⁺.

15D: 1-{[1-{Cyclohexy/methyl}-7-methoxv-1*H*-indɔl-3-yl|carɔcny|]-4-ethy-3-methylpiperazine, hydrochloride satt was prepared using 1-{1-(cyclhexy/methyl)-7-methxy-1*H*-indol-3-yl|carbonyl|-3-methylpiperazine. ¹H NMR (400MHz, CDɛOD) & 0.97-1.43 (11H m), 1.56 (2H, br d, J·12.0), 1.64-1.89 (4±, m), 3.12-3.68 (7H, br m), 3.95 (3H, s), 4.25 (2±, d. J·2.0), 4.50 (2F, br s), 6.77 (1H. d, J·8.0), 7.0 (1H, t, J·8.0), 7.26 (1H, d, J·8.0), 7.54 (1H, s). EIMS; m/z = 338.2 [M+H]*
15E: 1-{[1-(Cyclohexy/methyl]-7-methxy-1-1-hindol-3-yl|carbonyl|irens-2.5-d|methyl-15E: 1-{[1-(Cyclohexy/methyl]-1-1-hindol-3-yl|carbonyl|irens-2.5-d|methyl-15E: 1-{[1-(Cyclohexy/methyl]-1-1-hindol-3-yl|carbonyl|irens-2.5-d|methyl-15E: 1-{[1-(Cyclohexy/methyl]-1-1-hindol-3-yl|carbonyl|irens-2.5-d|methyl-15E: 1-{[1-(Cyclohexy/methyl-15E: 1-[1-(Cyclohexy/methyl-15E: 1-[1-(Cyclohe

4-ethylp perazine, hydrochloride salt

25 1-[[1-(Cyclohexylme:hy/)-7-methoxy-1*H*-Indol-3-y [carbony] trans-2,5cime-hybiperazine was prepared following the mathod in example 12, using 1(cydohaxylmethyl)-7-methoxy-indole-3-carboxylic acid and trans-2,5dimethylt iperazine. The procedure described under example 14 was used to afford

the fitte compound. ¹H NIMH (40¢MHz, CD₂OD) 5₄ 0.97-1.32 (9H, m), 1.37 (3H, t, J) 30 7.0), 1.44-1.32 (9H, m), 3.12-3.78 (6H, br m), 3.95 (3H, s), 4.17-4.33 (3H, m), 5.00 (1H, br s), 6.76 (1H, d, J7.5), 7.10 (1H, t, J8.0), 7.21 (1H, d, J8.0), 7.49 (1H, s). EINS; m/z = 412.4 {M+H}*.

itimethylciparazine, hydrochbride salt was prepared using 1-{[1-(cyclohexylmethyl)-35-firethoxy-1*H*-fincol-3-y]carbonyl]-3,5-firethylpiparazine and iodorrethane. ³H NMR (400MHz, CD₃DD) 8, 0.97-². 89 (17H, rr.), 2.56 (3H br si, 3.23-3.48 (4H, br rr.), 3.95

L)

(3H, s), 4.26 (2H, d, J7.0), 4.49 (2H, br d, J12.0), 8.77 (1H, d, J7.5), 7.10 (1H, t, J

S

10 15H: 1-{{1-{cyc:ohexylmethyl}-7-methoxy-}1HJndol-3-yllcarbonyl}-3,4-dimethyl)-3,4-dimethyl)-girationsy-14-indol-3-yllcarbonyl}-3-methylpiperazine and iodo methane. ¹H NMR (4Colvl)+z CD₂OD) 8, 0.97-1.89 (*4.4, m), 2.92 (5H, br s), 3.19-3.61 (5H, br m), 3.95 (3H s), 4.26 (2H, d. J.7.0), 4.49 (2.4, m), 6.76 (1H, d. J.7.5), 7.10 (1H, t. J.8.0), 7.27 (1H, d. J.8.0), 7.54 (1H, s), 3.84 2 (M+H)

15 (1H; 3, 78.3). 7.54 (1H, s). EIMS; m/z = 384.2 [M+H]*.

15I: (S-14**-(Cyclopent/Imethyl)-7-methoxy-1 H-Indol-3-yllearizonyl}-4-ethy/-2
Tieth/Mpiperazine, hydrochloride sell was prepared using {S-1-{{1-}}}

(cyclopantylmethyl)-7-methoxy-1*H*-indol-3-yl]sarsonyl]-3-me:hylpiperazine end iodoethane. ¹H NMR (400MHz, CD₈DD) δ_H - 24-7-42 (EH, m), 1.51-1.75 (EH, π), 2.43 (1-4, heptet, J.7.6), 3.12-3.23 (2H, m), 3.47-3.71 (EH, br m), 3.95 (3H, s), 4.38 (2H, d, J.6.9), 4.51 (2H, d, J.6.9), 4.51 (2H, d, J.6.2), 7.10 (1H, t, J.7.7), 7.26 (1H, d, J.6.2)

meth/plicerazine, 'nydrochloride salt was prepared using (:R)-1-{[1-67:30pertyln:ethyl]-7-methoxy-1H4ndol-3-yl]carbonyl]-3-methylpiperazine (prepared as detailed in example 12) and icdoethane. 'H NIMR (400MFz, CD₈OD) 5_H 1.24-1.42 (8+, m), 1.51-1.73 (6+, m), 2.45 (1+, heptet, J.7.6), 3.12-3.23 (2+, m), 3.47-3.71 (5-, br.n), 3.35 (3+, s), 4.33 (2+, d, J.6.9), 4.51 (2+, br.s) 6.77 (1+, d, J.8.2), 7.10 (1+, t, J.7.7), 7.26 (1+, d, J.6.1), 7.60 (1+, s). EIMS; m/z = 984-2 [4++]*.

2H, br mj, 6.77 (1H, d, J 7.5j, 7.11 (1H, t, J 8.0), 7.27 (1H, d, J 8.0), 7.56 (1H, s).

j2H, d, J7.6), 4 52 f2H, br d, J 14.6), 6.77 (1H, d, J7.9), 7.10 (1H, t, J7.7). 7.27 (1H, 2.43 (114, hepter, J7.4), 2.86-2.99 (314, m.), 5.17-3.60 (514, br m.), 3.95 (314, s.), 4.38 cdome:hane. ¹H NIMR (400MHz, CD₃OD) 5- 1.27-1.42 (5H, mj, 1.52-1.74 (6H, m), cyclope try methyli-7-methoxy-1 H-indol-3-yllcarbonyly-3-methylcicerazine and dmethytoperazine, hydrochloride sall was prepared using (Ri-1-ff!-

m

d, J(8.1), $7.60^{\circ}(11^{\circ}, s)$. EIMS; $m/z = 370.5 \text{ IM+HI}^{\circ}$.

131: [A)-1-[[1-(Cyclopentylmethyl)-7-methoxy-1 H-indol-3-vl]carbonyl-3,4-

4.61 (4H, m), E.77 (1H, 3, J7.9), 7.10 (1H, 1, J8.0), 7.25 (1H, d, J8.1), 7.53 (*H, s). ethylologiazine, hydrochloilde salt was prepared using 1-[1-(cyclohexylmethyl)-7-(400Ml-z, CD₃OD) δ_H 0.97-1.90 (20H, m), 2.32-3.69 (6H, or m), 3.95 (5H, s), 4.22rrelhoxy-1H-indol-3-ylycarbonyly-3,3-dimethyloiperazine and iodoethane. 1H NNIR ISM: 1-(11:(Cyclonexylmethy)-7-methoxy-1H-indo:3-ylcarbomyl-3,3-dimethyl-4-EIMS; m/z = 412.4 [M+H" 2

15N: 1-11-(Ovclohex/4methyl)-7-methoxy-1/Hincol-3-ylbzrtronyl)-3,3,4-

? rrethoxy-1 H-Indal-3-y]carbony}-3.3-dImethylpiperazine and iodomethane. ¹H NMR s), 4.22.4 60 (4H, m), 6.77 (1H, d, J7.7), 7.10 (1H, t, J8.1), 7.25 (1H, d, J8.2), 7.54 trimethyloperazine, hydrochloride salt was prepared using "-{[1-(cyclohaxytme:hyl)-(400MHz, CD₃OD) & C.98-1.90 (17H, m). 2.85 (3H, sj., 3.29-3.70 (4H, mj., 3.95 (3H, $(1H, s) E MS; m'z = 398.2 [M+H]^+$. ō

3.19-3.6 (5H. br m), 3.95 (3H, s), 4.26 (2H, d, J7.0), 4.49 (2H, m), 6.76 (1H, d, J iodornethane. 14 NMR (4001/Hz, CD₃OD) & 0.97-1.89 (14H, m), 2.92 (3H, br.s), (cyclor exylmethyli-7-methoxy-1. H-indcl-3-yl]carbonyl}-3-methylpicerazine and 150: (S)-1-[[1-[cyclohexylmethy]-7-methoxy-1H-indol-5-yllcarbom/i-3,4dimethylp perazine. Eydrochlotide selt was prepared using (S)-1-[[--20

oromo-2-fluoroethare. 14 NMR (400I/IHz, CD₃OD) 54 0.96-1.90 (14H, m), 3.31 -(S)-1-[[1-[cyclohexy|methyl]-7-methoxy-1H-indol-3-yl]carbonyl}-3-metryl-4-(2-3.50 (7H, br m), 3.95 (3H, s), 4.26 (2H, a, J 7.0), 4.40 - 4.59 (2H, m), 4.68 - 5.04 7.5), 7.10 (1H. t, J.8.0), 7.27 (1H, d J.8.0), 7.54 (1H, s). EIMS; m/z = 384.2 [M+H]. **1**1 fluoroethid/biperazine, hydrochloride salt was prepared using (cyclohexylmathyl)-7-met noxy-1 H-indol-3-yl[carboryl]-3-methylpiperazine 25 8

Example 16

EIMS; $n_i z = 416.0 [M+H]^4$

<u>(PL2-II1-(Cyclohexylme;hyl)-7-me;hoxy-1H-indo</u>L3-yljcarbonyl}-cctahydro-2Hcyridol 1,2-alpyraz ne 33

PAGE 25/36 * RCVD AT 4/20/2007 9:55:12 AM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/9 * DNIS:2730664 * CSID:19734227698 * DURATION (mm-ss):09-16

8.72 mm of) in dehibromethane (30 m) were added glycine methy ester hydrochloride (1.09 g. 8.72 mmol), 1-[3-(d methylam no)propyl]-3-ethyl carbodi mide hydrochloride (2.01 g. 10.46 mmol), 1-hydroxybenzotrazole (1.22 g. 9.04 mmol) and trieff-ylamine (2.42 ml 17.4 mmol). The mixture was stirred under a stream of nitroger for 18 hours. The resulting mixture was weshed with 0.5M hydrozhlorc acid (20 ml), wester (2 x 20 ml) and brine (20 ml), driac over sodium sulphate and concertrated to yeld (79.1-(teributoxycarbony))pipendine-2-carboxyglycine methyl ester as a colourless of (2.47 g. 8.23 mmol).

S

2

(R)-1-(Tertbutoxycarbonyl)plperidine-2-carboxyglycine methyl ester (2.46 g, 8.20 mmol) was dissaved in trilucoacetic acid (10 ml) and the resulting solution stirred for "hour The triflucroace:ic acid was then removed to yield a cotourless oil, which was dissolved in metranol (85 ml) and triethylamine (9.0 ml, 64.6 mmol) acided. The resulting mixture was heated under reflux for 4 hours. The solution was then concentrated to afford a pale orange cill which was recrystallised from heptane 46%, ether 48%, 2-proparol 4%, to yield (R)-cctahydro-1 4-dioxo-2.H-cyrido(1,2-alpyrazine 68 white crystals (0.66 g, 3.90 mmo)).

약

20 (*F*)-Octahydro-1,4-dioxo-2,4-pyrldo[1,2-a]pyrazine (0.5 g, 2.98 mmol) was added actrionwise to a stirred solution of lithium aluminum hydride (1M in tetrahydrofuran; 11.9 m, 11.3 mmol). The resulting mixture was heated under reflux for C.5 h. The solution was then cooked to 0°C and treated dropwise with water (1.35 ml). 1M socium hycroxide solution (0.45 ml), then water (1.35 ml). Tetranydrofuran (10 ml) was added and the solution stirred for 0.5 h, before filtration. The filter cake was washed will tetrahydrofuran (2 x 5 ml) and the combined filtrate and washings concentrated to yield (*R*)-octahydro-2.4-pyrldo[1,2-a]pyrazine as a yellow oil (0.29 g, 2.07 mmol).

To a solution of 1-(syclonexytmethyl;-7-methoxy-1+Hidole (0.49 g, 2.35 mmot) in 1,1,2,5-tetrachloroethane (2.5 m), was added oxelyl chloride (0.19 ml, 2.12 mmot) with silining under a stream of nitrogen. The mixture was heated at 120°C for 2 hours. After cooling to room temperature, triethylamine (0.30 ml, 2.13 mmot) was added, followed by (R)-octahydro-2H-byridol(1.2-a]pyrazine (0.28 g, 2.03 mmot) as a solution in 1,1,2,2-tetrachloroethane (2 ml). The solution was strind at room temperature for 2 hours. Solium hydroxide solution (1 M; 8 ml) was then added and the resulting mixture partitioned between clichloromethane (10 ml) and water (10 ml).

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PAGE 26/36 * RCVD AT 4/20/2007 9:55:12 AM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/9 * DNIS:2730664 * CSID:19734227698 * DURATION (mm-ss):09-16

To a solution of (A)-(-j-1-(tertbutoxycarbonyl)-2-piperidine carboxylic ecio (2.00 g.

[M+H].

8

sulfate and concentrated. The resulting purple cill was purified by flash chromatography using 38% dichoromethane, 2% methanol as eluent to yield the tille product as a pale brown oil (245 mg, 0.60 mmol), [o]₀²² +13° (c 1.87 mg/ml in CHCl₃); ¹H NMR (400M-2, CDCl₃) 5₆ 0.92-1.05 (2H, m), 1.12-1.36 (6H, m), 1.48-1.83 (9H, m), 1.83-1.58 (1H, m), 2.07 (1H, ct, J.1.5, 4.0), 2.24 (1H, dt, J.12.0, 3.0), 2.70-2.81 (3H, m), 2.84-2.86 (1H, m), 3.19-3.25 (2H, m), 3.93 (3H, s), 4.18 (2H, d, J.7.0) 4.18-4.32 (2H, m), 6.65 (1H, d, J.7.5), 7.07 (1H, dd, J.8.0, 7.5), 7.25 (7H, s), 7.29 (7H, d, J.8.0), EIMS m/z = 410.2 [M+H].

S

The organic layer was extracted, washed with water (10 mil), dried over sodium

0

Example 17

The procedure described under Ξ xample 16 was further used to prepare the following compounds:

17A. (S)-2-[[1-(Cyc.chexylmethyl)-7-methoxy-1*Hinc*lol-3-*A*]carbonyl-octahydro-2H15 Eyridc[1,2-3|Ey-azine, hycrochloride salt was prepared using (S)-(·)-1-(tertbutoxycarbonyl)-2-piparidire carboxylic acid. [d]₂²² -18 (free base; c 4.05 rrg/ml in CHCl₃);
¹H NMR (4COMHz, CDCl₃) & 0.99-1.08 (2H, m), 1.13-1.28 (3H, m), -.50-2.03 (12H, m), 3.02-3.12 (1H, rr), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.95 (3H, s), 4.27 (2H, d, J.2.0), 4.49-4.59 (2H, m), 6.77 (1H. d, J.7.5), 7.11 (1H, dd, J.8.0, 7.5), 7.27 (1H. d, J.8.0, 7.5), 7.27 (1H. d, J.8.0), 7.54 (1H. s); EIMS: rr/z = 410.5 [M4.H].

178. (R-2-fit-(Cyclobexylmathyl)-7-methoxy-1*H*-indo-3-yllcarbonyl]-oclahydro-2*H*-pyrrolof1.2-alpyrazine was prepared using (*R*)-(+)-1-(tertbutoxycarbonyl)-2-pyrrolidine carboxylic acid. ¹H NMR (400MHz, CDCl₃) &_H 0.92-1.04 (2H, m), 1.13-1.21 (3H, m), 1.40-1.45 (*F, m), 1.57-1.89 (5H, m), 2.00-2.1C (1H, m), 2.15-2.29 (2F, m), 2.76-2.85 (1H, m), 3.02-3.23 (3H, m), 3.93 (3H, s), 4.18 (2H, d, J7.0), 2.52-4.56 (2H, m), 5.57 (1F, d, J7.0), 7.09 (1F, 1, J8.0), 7.25-7.30 (2H, m); EMS: mz = 396.2 (M+-1]¹.

17C. (\$\insert{S}\)-24['-(Cyclohexylmethyl)-7-methoxy-1*H*-indol-3-ylkenbonyl-cctahyd \(\text{o-2}H\)

Payrolo[1,2-a]byyaz he, hydrochloride sall was prepared using (\$\insert{S}\)-(1)-1

(tertutoxycarbonyl)-2-pytrolidine carboxylic acid. \(^1\text{H}\) NM/R of free base (400l/Hz, CECle) \$\insert{b}_1 0.53-1.63 (2H m), 1.11-1.21 (3H, m), 1.35-1.46 (1H, m), 1.56-1.89 (5H m), 1.36-2.05 (1+, m), 2.21-2.27 (2H, m), 2.77 (1H, t, J.11.0), 8.07 (1H, d. J.10.5), 3.36-3.20 (2H, m), 2.33-3.30 (3H, s), 4.18 (2H, d, J.7.0), 4.26-4.41 (1H, m), 2.43-4.56 (1H, m), 6.65 (1H, d. J.8.0), 7.07 (1H, t, J.6.0), 7.25-7.30 (2H, m); ElMS: m/z = 396.2

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17D: (St-2-[II-(Cyc opentylmethyl)-7-methoxy-1H4ndol-3-yllcarbonyl-octahydro-2H-byndol 1 2-albyrazine, hydrochloride salt was prepared using (St-(+)-1-(erdbutoxycarbonyl)-2-plperid ne carboxylic acid and 1-(eyclopentylmethyl)-7-matnoxy-1H4ndole. ¹H NMR (400\lambda Hz, CD_aOD) & 1.27-2.03 (14H, m), 2.41 (1H, heptel, J7.0), 3.01-3.52 (7H, m), 3.95 (3H, 3), 4.38 (2+, d. J7.5), 4.52 (2H, d\lambda J, 10.0, 7.0), 6.77 (1H, d, J8.0), 7.1 (1H, t, J8.0), 7.26 (1H, d, J8.0), 7.6 (1H s). EIMS: m/z = \$86.2 [M+H]*.

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17E: (S.2-ff.-(Cyclopentyln-ethyl)-7-methoxy-1-Hindal-3-yllcarbcnyl)-octahycro-2H-pymolo 1 2-alpyrezine, hydrochloride salt was prepared using (S)-(·)-1- (te-fbutoxycarbonyl)-2-pymolidine carboxylic acid and 1-(cyclopentyln-ethyl)-7-methoxy-1*ft*-ndole. ¹-\text{NMR} (400M-z, CDCl₈) & 1.21-2.23 (15H m), 2.41 (1H, heptet, J7.5), 2.75 (1H t, J11.0), 3.01-3.20 (5H, m), 3.94 (3-4, s), 4.33 (2H, d, J.5), 4.32-4.53 (2H, m), 6.65 (°, H, d, J7.5), 7.07 (1H, t, J7.5), 7.23-7.21 (2H, m). ElMS; m2 = 362.2 [M--1]*.

2

15 17F: (35,979-2-[11-(Cyclohex/Irrethyl)-7-rrethoxy-1/H-indol-3-ylloarbonyl]-3isobutyloctahydro-2/H-oyrrolof1,2-aloyrazine was prepared using (36,979-octahydro-1,c-dioxo-2/H-pyrro of1,2-alpyrazine (commercially evalable) instead of (7)-

1,4-dioxo-2.Hpyrro o[1,2-a]pyrazinə (commercially svatable) instead in (n)oc.ahydro-1,4-dioxo-2.H-pyrido[1,2-a]pyrazine. EIMS; m/z = 482.2 [M-1]*.

17G: (3S,9S;-2-[[1-(Cys]ohexyImethyl)-7-methoxy-1.H-indoh-3-yllcatcon41-3-

20 rreflytoctahydro-2-h-oyrroloj1,2-e.boyrazine was prepared using 1-(tertbu:oxycarbony))proline and L-alanine mathyl ester hydrochloride salt. EIMS; m/z = 410.0 [M+H]*.

17H: (2R,cs)-1-ff (-(Cyclohexyhnethyl;-7-methoxy-1 H-indol-3-yl carbonyl]-2-fo-hzdroxylethyl-4-methylpperazine was prepared using 1-methyl-1-25 (tertbutoxycarbonyl)glycine and 0-threonine methyl ester hydrochloride salt. EMS:

m/z = 414.2 [M+H]*.

171. (2.S.o.R)-1-4[1-:Oxclorexylmethyl]-7-methoxy-1/H-indol-3-yllcarbonyl}-2-(c: hydroxylethyl-4-methylpiperazing was prepared using 1-methyl-1-(tertbutoxycarbonyl)glycine and to:theonine methyl ester hydrochlorice salt. EIMS; 3.3 m/z = 414.2 [M+H]*.

17.J.: (S)-2-f[1-(Cyclohexyknethyl)-7-mathoxy-1/H-indol-3-yl carboryl)-3.3-c|me:h/d-cyclohydro-2/H-pyrrolo[1,2-a]pyrazine was prepared using 1-(terrbutoxycarbonyl)-proline and arrinoisobutyric acid methyl ester hydrochloride sait. EIMS; m/z = 424.2

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Example 18

A

1-{[1-{Ovdohexylmethul-7-methaw-1/H-indo-3-{ficerboryl-3-{fill.comethul) piperazine, hydrochloride salt To a solution of 2,3-dib omograpionic acid ethyl ester (21.91 ml, 150.7 mmol) in tolurane (175 ml) at 40°C was added a mixture of M.M.-dicenzylethylenediamine (25.87 g., 149.2 mmol) and trie:hylamine (37 ml, 269 mmol) in tolurene (75 ml). The mixture was heeted to 80°C for 16 h, filteren and the precipitate washed with tolurene (200 ml). The combined filtrates were washed with water (2 x 200 ml), dried with magnesium sulfate and evaporated to afford 1,4-dibenzyl-piperazine-2-carboxylic acid ethyl ester (45.57 g) as an orange oil.

Lithium aluminium hydride († M solution in terrahydrofuran, 32 ml, 32 mmol) at 0°C was treated propyise with a solution of 1,4-dibenzyl-piperezine-2-carboxylic acid ethyl ester (10g, 32.1 mmol) in tetra-rychofuran (30 ml) and stirred for 16 hours. The m xture was quenched by slow addition of sodium hydroxide solution i4 M, 150 ml),

15 followed by dichloromethene (200 in l). The organic phase was separated, dried with sodium su fate and evaporated to afford 1,4-dibenzy-2-(sycioxymethy))piperazine (8.36 g) as an crange of.

To a solution of diethylaminosuliur trifluoride (1.5 ml, 12.16 mmol) in dichlorome:hane (10 ml) at -72°C was added 1,4-d.benzyl-2-(hydroxymethy)piperazine (3 g. 10.1

whilst warming to room temperature and treated with water (20 ml). The aqueous phase was basified to phree using 4 l/ sodium hydroxide and the organic phase separated to phree settacted with dichloromethane (2 x 30 ml) and the corr bined organic layers dried with sodium sulfate and evaporated. The residue was purified by flesh chromatography eluting with 20% (v/v) eithy acetate in hexane to afford 1,4-diberzyt-2-(illucromethy))piperazine (2.94 g) as a colcurless oil.

To a stury of pelladium on carbon (10% v/v/w, 1 g) in ethanol (20 ml) was added 1,4-

dibenzy!-2-(fluoromethylipiperazine (2.58 g, 13 mmol) in athanol (20 ml). The mixture was heated to 65°C under an hydrogen atmosphere (5 stm.) for 72 hours, filtered through dicalite and the dicalite washed with ethanol (50 ml). The filtrates ware evaporated to afford 2-(fluoromethylipiperazine (0.87 g) as a colourless solld. To a solution of 1-(cyclohexylimethyl-7-methoxy-indoe-3-carboxylic acid (0.59 g, 2.04 mmol, prepared following the method in Example 1) and 2-(fluoromethyl) placeazine (0.37 g, 3.15 mmol) in cichloromethane (15 ml) was added 1-(3-64 mmol) and 1-65 almethylaminopropyl)-3-ethylcarbodii-nide hydrochbride (0.47 g, 2.45 mmol) and 1-65 almethylaminopropyl)-3-ethylcarbodii-nide hydrochbride (0.47 g, 2.45 mmol) and 1-65 almethylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 ml) was added 1-(3-65 mmol) and 1-65 mmol) and 1-65 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 ml) was added 1-(3-65 mmol) and 1-65 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 ml) was added 1-(3-65 mmol) and 1-65 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 ml) was added 1-(3-65 mmol) and 1-65 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 ml) was added 1-(3-65 mmol) and 1-65 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 mlothylaminopropyl)-3-ethylcarbodii-nide hydrochbride (1.5 mlothylaminopropyl)-3-ethylaminopropylaminopro

hydroxy benzotriazo'e (0.07 g, 0.51 mmol). The mixture was stirred at room

emperature for 18 h and evaporated. The residue was purified by flash

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title comparent (free base) as a colourless oil (0.47 g). The free base (0.05 g) was dissolved in diethyl either (3 ml) and treated dropwise with 2 M hydroch oric ac din diethyl either (1 ml). The resu ting prec pitate was collected by filtration, washed with diethyl either (10 ml) and dried under reduced pressure to afford the title compound (1:1 hydrochloric acid sall) as a colour ess solid (0.05 g, 0.12 mmol). 'A NMR (400MHz, CD₃OD) & C.96-1.27 (5H, m), 1.57 (2H, br c, J.12.9), 1.63-1.90 (4H, m). 3.21-3.53 (4H, m), 3.68-3.79 (1H, m), 3.35 (3H, s), 4.26 (2F, d, J.7.1), 4.43-4.82 (4H, m), 8.77 (1H, d, J.7.2), 7.21 (1H, t, J.7.5), 7.27 (1H, d, J.8.0), 7.57 (1H, s); EllifS: m/z 270.2 [Fragment+Hf].

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chromatography eluting with 0-10 % (v/v) methanol in dichic mmethane to afford the

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Example 19

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1-f[1-fCyclo rexylmethyll-7-methov-1-Hindol-3-yf carbonyll-3-f(fl.oromethyl)-4-cyclopropyl piperazine, hydrochlor de salt

(fluoromethyt) piperaz ne (0.2 g. 0.52 mmol, prepared folkwing the method in Example 18) in methanol (10 ml; was added acetic add (C.18 ml; 3.1 mmol), 4Å molecular sieves (1 g), [(1-ethoxycyclopropyt)axy] trimethytsilane (0.62 ml, 3.1 mmol), and sodium cyanaborohydride (0.15 g, 2.33 mmol). The mixture was heated to 70°C for 18 h, filtered and the precipitate washed with dichloromethane (20 ml) and

methanol (20 m). The fitnetes were evaporated, dissolved in dichloromethane (30 m), and washed with sodium hydroxide solution (4 M, 15 m) and saturated sodium chicride solution (15 m). The crganic phase was dried with sodium sulfate, evaporated and the residue purified by flash chromatography eluting with 2 % (v/v) methanol in dichloromethane to afford the title compound (free base) as a yellow oll (3.2 g). The free base was dissolved ir diethyl ether (3 ml) and treated chopwise with

by filtration, washed with diethyl ether (10 ml) and dried under reduced pressure to afford the title corrpound (1:1 hydrochloric acid salt) as a colourless sofid (0.2 g, 0.43 30 mmol), ¹H NMR (400MHz, CD₂OD) 6, 0.91-1.25 (9H, m), ⁻ .57 (2H, br d, J 12.6), 1.82-1.81 (4H, m), 2.8-2.93 (1H, m), 5.33–3.82 (5H, m), 3.56 (3H e), 4.27 (2H, d, J 7.0), 4.45-4.86 (3H, m), 5.13-5.31 (1H, m), 6.77 (1H, d, J 7.3), 7.11 (1H, t, J 9.1), 7.26 (1H, d, J 9.1), 7.56 (1H, s); EIMS: m/z 428.2 [M+H][†].

2 M hydrochloric acid n diethyl ether (1 m). The resulting precipitate was collected

Example 20

in-vi;ro determination of efficacy and potentry at the human CB1 receptor expressed in CHO cells

2

5 Chinese Hamster Ovary (CHO) cells expressing the human CB1 receptor and a budierase reporter gene were suspended in phenol red / samm tree DMEM / F-12 mt max containing perfellin / streptomycin (50U/50 µg/ml) and fungizore (1 µg/ml) and seeded into 95 well plates at a density of 3 x 10° cells per well (100 µl final volume).

Celis were incubated overnight (approx. 18 h et 37°C, 5% 00z/95% air) prior to assay.

The test compound (10mM solution in DNSO) was diluted in F12 ML1 Mix to give a range of stack solutions from 0.11 mM to 0.11 mM. The stock solutions (10µ) were added directly to the relevant wells. The plates were incutated at 37°C for 5 hours to allow agonist-induced expression of the luciferase enzyme. Under subdued light, LucLite substrate (Packard; reconstituted as per manufacturer's instructions; 100 µl) was added to each well. Plates were covered with Top Seal and then incubated at room temperature for 5 minutes before counting on the Packard TopCount (single Ehoton counting, 0.01 minute count time, 5 minute count delay).

A 'best-fit' curve was fitted by a minimum sum of squares method to the plot of counts per second (CPS) against compound concentration (M) to obtain an EC₅₀ value. Table 1 shows the pEC₅₀ values obtained for some representative compouncs of the invention.

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1-[[1-{Cyclopentylmethyl};-7-nethcxy-1;+	Example	Example Chemical name	Chemical structure	PECE
	2	1-[[1-{Cyclopentylmethyl;-7-methoxy-1/-	ه ا	6.5
hydrochloride seit 1-{{1-{Oyolof-exylmethyli-7-methoxy-1,H-indol-3-ylcarbonyl}-4-{2-hydroxy-ethyl) alperazine, trifluoroacetic ecid salt -{{1-{Oyolo*exylmethyli-7-fluoro-1,H-indol-3-ylcarbonyl}-4-ethylpiperazine, hydroculoride salt		indol-3-y]carbonyi, 4-ethylpiperazine,		
1-[[1-(Oyclor-exylmethyl]-7-methoxy-1,H-indol-3-y]carbonyl]-4-(2-hydroxy-ethyl) siperazine, trifluoroacetic ecid salt -1[1-(Cyclor)exylmethyl)-7-fluoro-1,H-indol-3-y]carbonyl-4-ethylpiperazine, hydroculoride salt		hydrochloride sait	• \$>	
indol-3-yl)carbomyl]-4-(2-hydroxy-ethyl) siperazine, trifluoroacetic ecid salt -{[1-(Cyclo hexylmethyl,-7-fluoro-1 H-indol-3-y]carbony}-4-ethylpiperazine, hydroculoride salt	30	1-{[1-{Cyclor-exylmethyli-7-methoxy-1#-	£	99
ethytholperazine, trifluoroacetic ecid salt -{II-iCyclohexytmethythy-7-fluoro-1H-indol-3-y certony.}-4-ethytpiperazine, hydroculoride salt		indol-3-yl]carbonyl]-4-{2-hydroxy-	₹°	
indol-3-y]:carcony}-4-ethylpiperazine,	•	ethyl) siperazine, trifluoroasetic ecid salt		
}	88	-{I1-iCyclohexylmethyl}-7-fluoro-1H-	کی پیکا پیکا	7.0
\(\frac{\}{\}\)		indol-3-y']:carcony.}-4-ethylpiperazine,		
- r		hydroc:noride sail	• •	

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1.2	رن ۲	ය ග	0.0	7.5	7.6	7.9	7.6	7.5
50	5.0	\$						
(+)-1-[[1-(1-Cyclohexylelhy])-1 H-indol-3- yilearbor yil-4-etityipiparazine, hydrochloride sait	1-{[1-;Cyclonex-3-enylmethylj-7-metfoxy-1;Hndol-3-yl[carbonyl]-4-ethyt;perazine	1-([1-(Cyclonexylmethyl)-E-fluoro-1.H-inclot-3-yl]carbony]-4-methylpiperazine, hydrochlorice salt	1-{{1-;Oyclonexylmathyl}.7-methoxy-1 <i>H</i> -incloh3-yl}cartony'}-3,5-dimethyl-4-ethyt-iperazine, hydrochloride satt	[[1-icyclohexylmethyth-7-methoxy-1 <i>H</i> -incol-3-yl]zarbonyl}-3,4,5-timethylpiperazine, hydrochlorine salt	(S)-1-{[1-(cyclohezylmethyl];-7-methoxy-1 H-ndol-3-y]carbonyli-3,4-dimethylpiperaz ne, hydrochloride sel:	(S)-2-(I1-(Cyc ohexylme:hyl)-7-me:hoxy- 1 H-indol-3-yljca:bonylj-octahydr:>2H pyrido-(1 . 2-a]pyrazine, hydrochloride salt	(S)-2-([1-(Cyc ohexylme:hyl)-7-me:hoxy- 1 h-indol-3-yl ca bonyl -octahydro-2# pyrrclo-[1, 2-a]pyrazine, hyd:ochlorice salt	(S)-2-[[1-(Cyclopentylmetryth-7-metroxy-1H-indol-3-y]]carbony/j-octahydro-2H-pyrldc-[1, 2-a]]pyrazine, hydrochloride salt
IŞ-(+)	Ċ	51	र	:: ::	150	17A	170	17 C

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Example 21: Tall Rick Latency in Mice

Mice were trained to sit still in a tail flick apparatus (Ugc Bas la, Italy) whilst tail flick latency was measured. The tall was exposed to a focused beam of redient heat at a 5 point approximately 2.5 cm from the tip. Tail flick latency was defined as the interval between the appliance of the thermal stimulus and withcrawal of the tail. A 12 second cut-off was employed to prevent tissue damage. Four groups of eight mice were treated with vehicle of one of three doses of the test compound, administered intravencusty (vehicle: saline 9 gil; Injection volume 10 in this). Tail flick latency was the measured before administration of the test compound administration. The ED₅₀ was calculated at T_{max}.

The compounds of examples 14, 15F, 15O, 17A, 17C, and 17D significantly increased the tail flick latency with an ED₅₅ < 5 LmoVKg.